

ACADEMY
FORUM
First of a Series

HOW SAFE
IS SAFE?

The Design of
Policy on
Drugs and
Food Additives

NATIONAL ACADEMY OF SCIENCES
Washington, D.C.
1974

A System-Analytic Viewpoint*

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Indeed, it is true that anyone who tries to deal with health in economic terms, which is a necessary part of a system-analytic point of view, is exposing himself to the risk of misunderstanding and even of bodily harm from outraged citizens. In a free enterprise society we can defend the incentives needed to reinforce the work-ethic in terms like depriving the poor of caviar and champagne; but we balk at cold-bloodedly depriving them of an artificial kidney or of a life-saving drug when these therapeutic benefits have become validated and available to the wealthy. Public attitudes about accelerating the availability of new drugs for anyone's benefit are more ambivalent, involving a conflict of values. This is precisely why we came together for this Forum.

The arousal of conscience about health is one of the major impulses toward more egalitarian redistribution of income, an ideological issue often confused with the technical ones of drug safety and of efficacious organization of health services.⁽¹⁾ The question of the proper dollar equivalent of a human life also often

* This text is an edited version of the transcript of the address as presented at the Forum. I spoke from rough notes at that time, and other exigencies detained me from preparing a more definitive statement without unduly delaying this publication. A more carefully argued and documented version will be published elsewhere and may well show signs of further evolution in my views.

--Author

(1) At least the canons of welfare economics separate the allocation of investments for a potential pareto optimum from the redistribution needed to achieve goals of social justice. The latter is the task for tax legislation or welfare assistance. However, political optima are not automatically achieved; in the real world some sacrifice of ideal productivity may be essential to achieve the political harmony which is in turn indispensable for economic efficiency.

comes up in these discussions; to my view, most such calculations are absolute nonsense.

The net crude social value of an individual's life is measured economically by the effect of his death on the net products left to the community. Calculations based on his still unrealized earnings are faulted by their neglect of the individual's consumption. To the extent that the worker has struck a fair bargain with his employers and with the Internal Revenue Service, he will on the average be consuming approximately what he is worth. We would have to conclude that the average net social value of a life is approximately zero!

Individual cases will show wide excursions, even short of the incalculable values attached to the lives of saints or dictators. Estate taxes will have been discounted in workers' bargains; but their premature collection is a social benefit. By this logic of the absurd, so is the demise of a superannuated beneficiary of Medicare. On the other hand, the death of the exploited worker who may consume less than his individual product would be a social loss, except when he is readily replaced in a less than full employment economy. We do not, in fact, deal with our fellowmen simply as units of production; these calculations take no account of the costs incurred by "nonproductive" survivors such as spouses and children. Since we have incurred a social obligation for their welfare, the transfer of their support to the community generates a social loss upon the death of a provider. (These losses already will have been socialized through the taxes incurred on wages during viable employment.)

From another angle we can see that each generation is subsidized by the undepreciated capital savings of its predecessor--its farms, houses, factories, fortresses, and libraries--and taxed by the depletion of unrenovable resources. If an economic measure is possible in these terms, the tangible values of human life might be calculated closer to the loss of anticipated future savings rather than of earnings.

All of these calculations of crude social value of life aggregate the interest of the community, but they ignore the welfare of the most interested person, namely the decedent. We are a society composed entirely of prospective decedents. Indeed, the collective aversion of risks of death and disease is a central function of social organization. From this standpoint there can hardly be a "proper" absolute value of life; we go through economic calculations only in order to achieve the most efficient relative allocation of resources in protecting our most precious goods. It may be misleading to use dollars as the currency for these evaluations. But unless we have some common measure for assessing risks, we will be spending disproportionate parts of our concern and energy for isolated parts of the overall problem of life, while neglecting others possibly more important. Our analysis is then entirely dedicated to helping us optimize the bargains that we need to make in gambling against fate.

In another context I have tried to estimate the dollar hazards of radiation side-effects in connection with the controversy about nuclear power. This calculation needed two estimates. The kind of dollars-for-health bargain that we strike in other contexts is a social judgment that can be observed rather than edicted. The health consequence of a given dose of radiation is a technical judgment about which there is a more convergent consensus than one would guess from a debate that has mixed it with social prescriptions. For the former I postulated that we might be willing to double our health expenditures for 20 percent improvement in health. This would imply a social willingness to invest \$400,000 to prevent a death, which is at the high side of present day political judgments. The latter is too complex to detail here.⁽²⁾ I found that a number like \$100 per person per rem exposure

(2) See J. Lederberg, "Squaring an Infinite Circle: Radiobiology and the Value of Life," Bulletin of the Atomic Scientists 27 (September, 1971): 43-45; and L. A. Sagan, "The Human Costs of Nuclear Power," Science 177 (August 11, 1972): 487-493.

came close to the intersection of many different actual policies which we use in coping with radiation exposure. For example, this says that the natural background of radiation already inflicts a per capita health cost of about \$10 per year, and that we also pay about \$5 in health side-effects (about the same in dollars to the radiologist) for our medical diagnostic X-rays. Generally, we expect X-ray diagnosis to be an advantageous bargain, although not of course when there is avoidable exposure to radiation without corresponding medical benefit.

People could quarrel with these numbers, but they might then be impelled to apply whatever number they arrived at consistently to a variety of policy decisions. If one could do as well with drugs and food additives, we would be much closer to a rational foundation for regulatory policies. The results of my personal inquiry remain primitive and elusive; and I feel a bit of a fraud in using the term system-analytic in my title, except insofar as a view is mostly in the eyes of the beholder.

We are in deep trouble both on the cost and benefit side at a primary level, and even worse when it comes to judging the impact of possible diseconomies of investment and innovation in the field of drugs and environmental additives.

A pricing of benefits for food additives is theoretically straightforward, and I cannot agree with Dr. Wescoe that we would discard a flavor or a color on account of any risk no matter how slight. We would have to discard every additive automatically and out of hand. For there simply is no way to assure that the risk of any substance or process is really zero. When one refers to zero risk he usually has some practical level of risk in mind, and it is our task to make such calculations explicit. Only then can we make the trade-offs rational and our policies publicly persuasive.

The pricing of food additive benefits is not just their annual market value, about \$1/2 billion a year, although this is one term in the equation. The consumer's net benefit is measured by the difference in the price of his purchases with and

without the additives, if he is indifferent to their presence, plus or minus his market judgment⁽³⁾ of their value when he knows they are there. Many additives are substitutes for natural food substances over which they may have only marginal economical advantage. For these the consumer benefit is much smaller than the size of the market and may approach zero. Others effectively reduce the price of food, for example by retarding spoilage or allowing convenient formulations not otherwise attainable. The production of food entails its own risk of life; hence to eschew economic advantages in the face of "any risk" may be as inhumane as it is inefficient. The reasonable question to ask is whether the benefits of a particular additive are commensurate with its possibly insidious risk to health. We need to bring these estimates out on the table, and of course they must be particularized substance by substance.

If the consumer also had the information to judge these risks, as well as consult his tastes, we might let the marketplace take the role of the Food and Drug Administration. The consumer could then calculate his own dollar equivalent of the implied risks. But we democratically have decided to collectivize such decisions. Against the lost advantages of the pricing mechanism, we must weigh the cost of putting this information into every consumer's hands product by product; his vulnerability to persuasion by mass advertising; and the disorganization of consumer interests as compared to producers', except via government. (Indeed the most perplexing issue in my reading of welfare economics is the role of advertising which is dedicated to the production of wants rather than of goods.)

(3) But here's the rub. The concept of the "consumer's surplus" is easier to enunciate than is any practical measurement. We have no laboratory where the price-elasticity of demand can be empirically measured without the intervention of a host of confounding factors. But most economic theory is based upon similar operationally inaccessible idealizations.

When we turn to drugs we face even more perplexing problems of assessing their benefits, since life and health are prominent terms on both sides of the equation. To start with, however, we can ask how drug prices are in fact determined and on what relationship to consumer benefits and the usual mechanisms of the marketplace.

Drugs cost so little compared to other health services (about 10 percent of health care expenditures) that I suspect their pricing is more akin to that of the cosmetics and the perfumes which accompany them at the retail counter than the pricing of tangible articles of commerce such as bread and automobiles. Howbeit a small private "tax" on these sales, less than you pay the government on your tobacco and your alcohol, supports the research and development of the drug companies in their competitive efforts to produce new products for the benefit of the consumers, and for their own benefit in beating out their fellows. At these prices a significant part of the cost of a drug may in fact not be its retail dollar price but its unwanted side-effects. We must learn to measure these for equity to the consumer and for assurance that we do not waste the precious resource of exposure to risk without achieving commensurate gains. In fact, we are in a sense trying to find the "optimum" number of casualties that should be associated with the use of new beneficial agents.

We could claim to aspire to zero risk, but this is unachievable in the real world. If that seems harsh, and this is precisely the analogy that has been used before, try to think of the ways that the automobile casualty rate could be reduced to zero. Of course, in principle it could be: for example, if a policeman on every block kept our speed down to a few miles per hour and periodically checked the state of our blood alcohol. But there is no way short of a total ban on new drugs or a system of infringement on personal behavior comparable to the analogy

that I mentioned for the automobile through which we can achieve perfect safety or even predict and anticipate every possible side-effect.

Our problem is to find a point of balance in the costs and benefits of drugs not where the advantage of a drug exceeds its price plus its hazards, which may always be true, but where further investment in development no longer leads to a commensurate yield in the aversion of risk and the enhancement of efficacy.

This is the familiar concept of marginal utility applied to drug development, and we should not be bedazzled by the undoubted absolute benefits of many drugs in seeking to find the optimal position of investment that must be made in verifying their efficacy and their safety.

Part of the investment cost is the deferral of benefit from the use of a drug while awaiting the outcome of further testing. This includes patients' benefits as well as producers' profits. For major therapeutic discoveries, such as some antibiotics, this cost conceivably could outweigh all the others; but I am confident that this is already in the minds of the regulatory agencies as well as of the other parties to these concerns.

A crude model of the drug R&D process is summarized in Figures 1 and 2. For these printed versions, extensive captions take the place of the pointer talk at the oral presentation.

Figure 1 is an idealized version of progressive investment in a drug research program. In reality it would be more appropriate for the engineering design of an electronic component, for it supposes the opportunity of progressive chemical modification leading to an ever better product. This hoped for objective improvement is measured by the net utility, the therapeutic benefit less the drug cost and less side-effects. The estimates of these parameters are subject to considerable uncertainty, expressed in Figure 2 as probability distributions. Especially since the Kefauver amendments, a very large part of drug research investment is

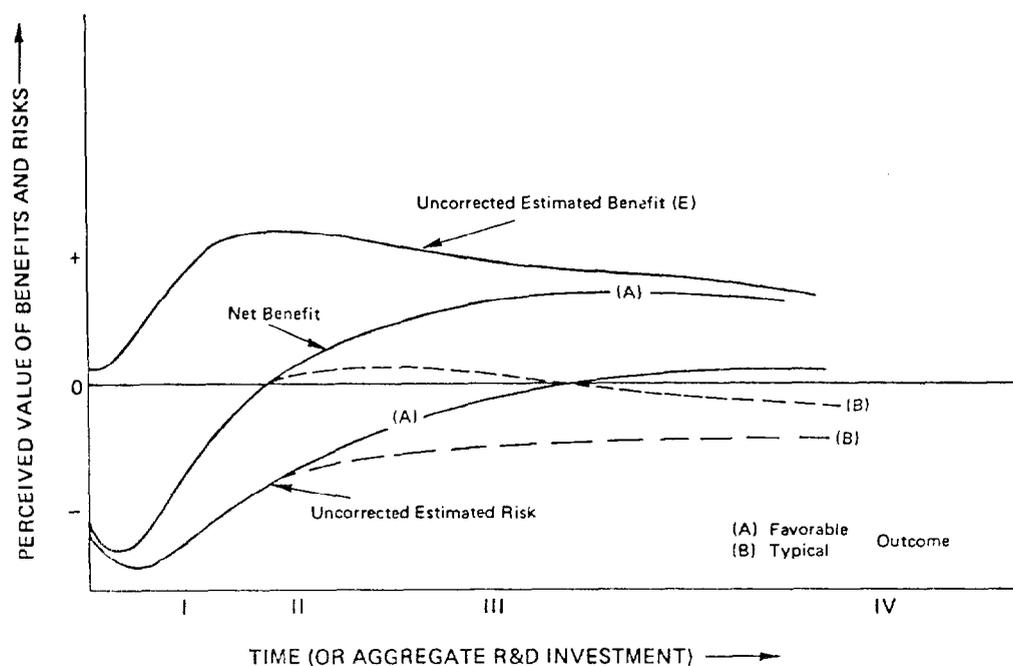


FIGURE 1: *Time course of a hypothetical drug development project.* Neglected are the costs of drug production, variances in the estimates (see Figure 2), and decreases in benefit because of the time value of money and of delayed patient access to the drug.

At point zero (no empirical data yet) there is a negligible presumption of utility and some presumption of risk. At I, evidence of specific biological activity should deepen the suspicion of risk. But a successful drug discovery will move to II, where further chemical refinement as well as knowledge of proper dosage, etc., reduces the risk, and the benefits can be foreseen. However, net benefit can still increase with further investment. This can, of course, also result in more efficient production processes and in turn lower the consumer's cost. R&D should continue to point III, where the slope of the net benefit curve equals the rate of investment. If continued to IV, there is a diminishing return with asymptotic refinement of the risk estimate.

Meanwhile, the gross benefit may fluctuate also. In this case, it may even decline with time owing to the eventual introduction of competing substitutes.

The drug might rationally be accepted at any point after II (but see Figure 2). Further R&D may be necessary mainly to determine whether the drug continues to confer net benefits relative to potential substitutes (compare cases A and B). At issue is the relative social utility of more information about this product compared, e.g., to research investments in a "next generation" of other substances. Unless safety is somehow monetized, the market mechanism may not motivate such investments. The impetus is left either to government or to the professional prescribers—and the latter's time may be too costly for unorganized responses to be effective.

The real payoff of further safety research is the discovery of unsuspected hazards that may lead to disapproval of the drug. This social gain is, of course, in direct conflict with the interest of the promoter who by now has invested much sweat, tears, money, perhaps even blood in the project.

Further delay in the introduction of products might be mitigated if we had other ways to ensure the vigilant scrutiny of a drug by disinterested parties after it has been marketed. The hazard is that by now the promoter may have trebled his investment between R&D and marketing. The shrewdness of drug developers in anticipating the further course of their investigations of safety and of benefit will, of course, have an enormous impact on the average development cost per successful drug that reaches the market. Equally contributory will be the style of the regulatory agency in posing criteria for acceptance that are relevant to the social utility of the drug's introduction.

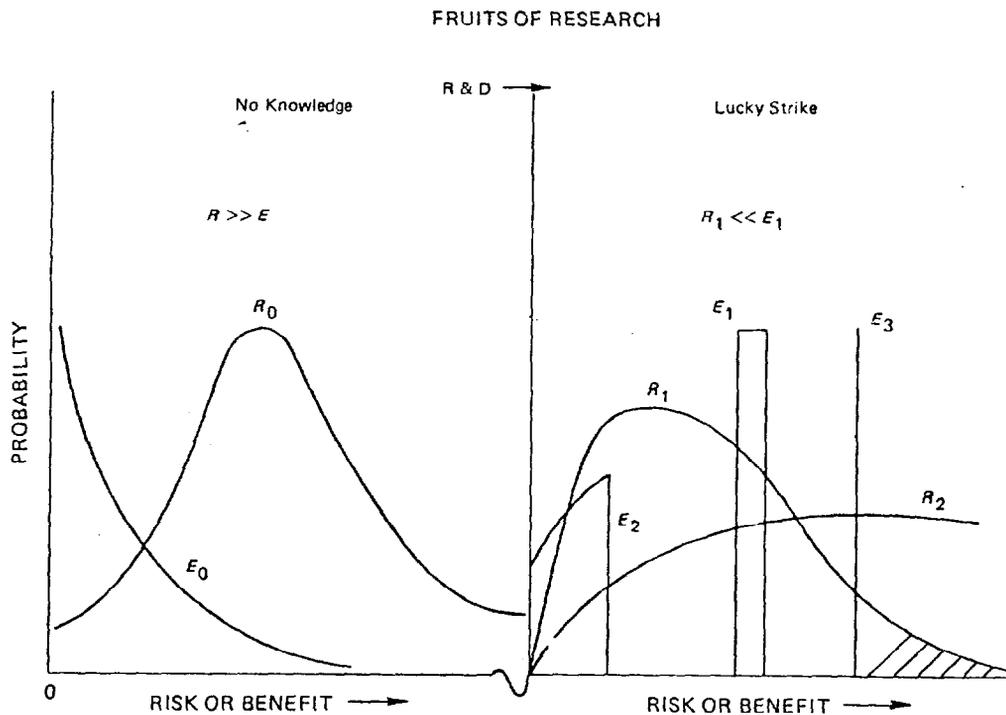


FIGURE 2: Probability distribution of risk and efficiency in a successful case. E_1 and R_1 on the right correspond to point II of the previous figure. The efficacy E_1 is assumed to be known with great precision in the context of controlled trials. However, this is an idealization for most drugs when alternative therapies are also considered. Besides the residual uncertainty in the risk distribution R_1 , the regulator must also take account of real-world degradation in the criteria and conditions of use of an approved drug, which may correspond to E_2 and R_2 . To assure a net social gain, he may demand that the more stringent criterion E_3 be satisfied. The patients of superior doctors are doubtless penalized in this way by the performance of the less qualified because of the lack of effective monitoring on prescribing behavior.

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concerned with the validation of a product in which the promoter already has a high stake, rather than the work leading to its primary discovery. Part of our task is to determine the optimum allocation of resources between these creative versus critical efforts. Our social policies must give priority to first order consumer benefits and risks. But we cannot neglect the incentives and rewards needed to motivate producers to risk their fortunes in seeking new drugs from which future consumers may also benefit.

Insofar as drug research tends to become ever more costly as it moves from the chemical laboratory bench to animal testing and to clinical trials, the early anticipation of possible faults can have an enormous influence on the efficiency of the research process. I am not aware of any systematic analyses of the allocation of research resources within the drug industry to these various stages of development. Dr. Gerald Lauback, president of the Pfizer Company, has commented that the batting average of success in new drug applications varies considerably from company to company. I would surmise that this is in part a consequence of the shrewdness of research strategies. However, other factors, such as accidents of change of policy with time or the different criteria applicable to drugs in different fields, may also play a very important role. In any event, one can hardly assess the cost-efficiency of the regulatory procedure without also addressing the pragmatic efficacy of the industry's response to it. In fact, the most passionate complaints that have been voiced from industry sources have been addressed not so much to the principles of drug regulation itself, which have become accepted parts of social policy to a very large degree, but rather to the bureaucratic framework in which these policies are actually implemented. But this also is a subject about which it is obviously difficult to obtain credible information for public scrutiny or to arouse public attention.

Once a drug has been developed to the point where it appears to be a promising candidate for more detailed benefit and risk evaluation, it is submitted to the critical process which is symbolized by Figure 2. Many other candidates, of course, fall by the wayside, but there are few public statistics to help us fit numbers to the parameters of our system design. Our prior state of knowledge about a compound likely to be found in the inventory of a drug company is that, having some biological activity, it is quite likely to be harmful; we can hardly posit that it would be useful without further studies. When it has reached the point of nominal acceptability, the probable benefit exceeding the probable risk, the distributions describing these parameters may resemble E_1 and R_1 respectively of Figure 2. Within the framework of a controlled trial the benefits may be rather well understood; and I have indicated this by showing E_1 as a spike with negligible variance. Risks tend to be more elusive to evaluate, especially the long-term side-effects, such as cancer or mutagenesis, which are such an important preoccupation today. R_1 is therefore indicated with a higher dispersion. Provided one has evaluated E_1 and R_1 not in a vacuum, but in relation to other therapeutic alternatives already available, the acceptance point for a drug rationally should be just when its aggregate benefits exceed the aggregate risks.

In practice this would be highly unpersuasive to an official with regulatory responsibility for a number of reasons, some of which are socially beneficial and some merely characteristic of the bureaucrat's environment. To take up the latter first, it is perfectly obvious that his calculus of risks must include his far greater vulnerability for criticism if the expectations, however reasonable, of risks $>$ benefit should fail; politically they will not be balanced as they are statistically by an equal number of circumstances where the contrary holds. Therefore, to protect his own position he is sure to demand a much more rigorous criterion than would be necessitated by an analytical view of social welfare. His characteristic management tool for this purpose is simply delay.

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This bias is strongly reinforced by more rational arguments of public interest. The inertia of drug replacement, particularly within a given firm, is such that the early approval of a barely adequate agent may delay the effort needed to bring about far superior introductions. Experience has shown a secular trend favoring early optimism and later disillusion for many drugs. Once the drug has been approved, the information gathering environment will be altered, sometimes irreversibly. Finally, it is necessary to extrapolate from the statistics derived from controlled clinical trials to those which will pertain when the drug is generally available. With rare exceptions this must result in a considerable deterioration of the benefit-cost ratio, if for no other reason that in the real world therapeutic environment the drug will be used in more complicated cases and sometimes by less critical prescribers. These shifts are indicated by the curves E_2 and R_2 ; the regulator is certain to require a shift in the criterion relative to risk represented by E_3 . At the present time we have no common understanding, much less agreement, about the appropriate size of that shift even in principle. This is, of course, further confounded by the practical difficulties of arriving at numbers to match these general concepts. The fact remains that drug developers are working in a policy vacuum with respect to the criteria that their products are expected to meet. The concept "safe," so blithely mentioned in law and in popular discussion, remains an essentially subjective judgment relative to possible benefits.

Figure 3 addresses a more technical problem with respect to the assessment of risk. Routine toxicological screening is likely to eliminate those agents showing a high order of toxicity. If by chance man should prove to be an unusually susceptible species, this also will be discovered during clinical trials or soon after the introduction of a new agent. Existing procedures appear to be well adapted to identifying such high level risks, and in the absence of unusually bad luck will

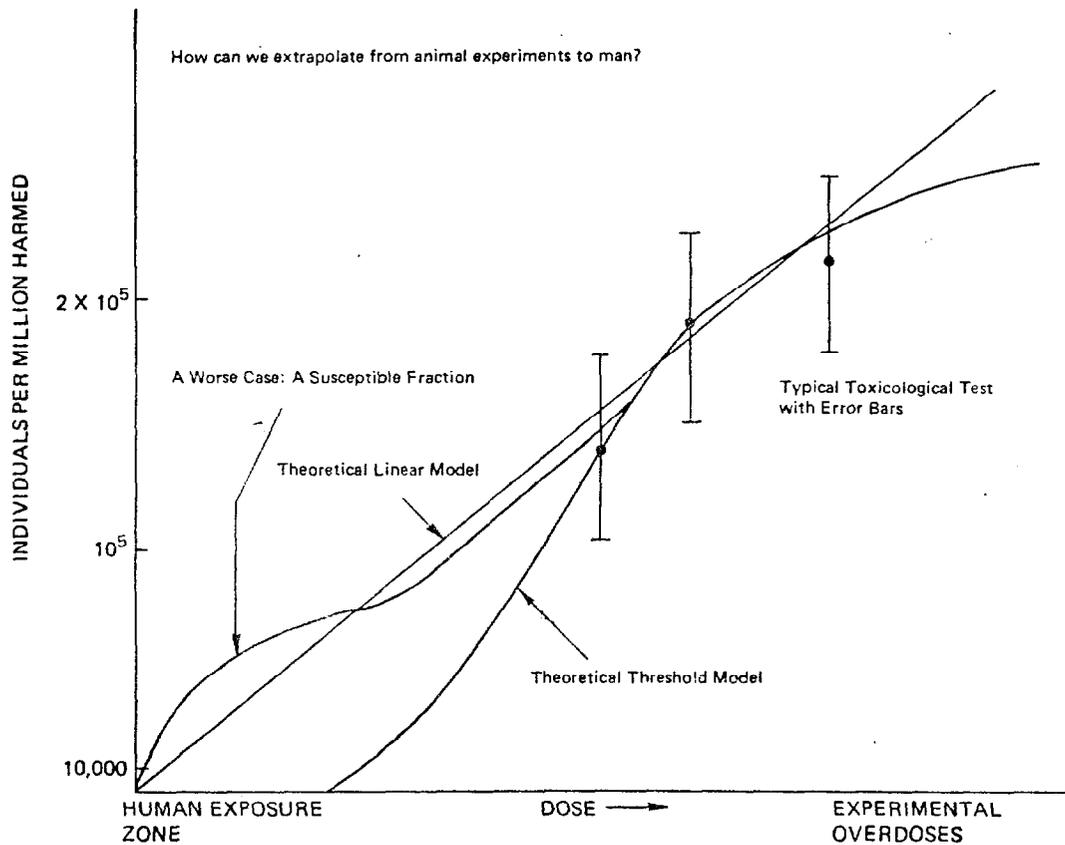


FIGURE 3: A hypothetical example of testing for the safety of drugs under conditions of calculated overdoses. It is difficult to do animal experiments where fewer than 10 percent of the animals respond. In order to satisfy this criterion, it inevitably may be necessary to use levels of a drug (or food additive) far in excess of that which would pertain to human usage. The most reasonable estimate of the level of human response is then highly dependent on the model adopted for drug effect as a functional dose. The arrow-bars shown on the two experimental points are not unreasonable for practical experimentation and might indeed be relatively even larger at lower levels of effect. Therefore, the failure to discover a toxic effect on a limited number of animals at a lower dose is unable to prove the safety of the agent for widespread human consumption, and we must rely on some theoretical rationale, or on experimental evidence, for the dose-effect model. For most purposes, the linear model may be appropriate in the absence of other knowledge. In some circumstances a threshold model can be justified which would be reassuring with respect to human susceptibility at lower doses. On the other hand, the occurrence of a minority of individuals with unusual susceptibility is an alarming alternative. This susceptibility may be the result of genetic variation, interaction with other drugs and environmental agents, or the disease states themselves. While data from drug overdoses may lead to distorted estimates of the safety of an agent, errors in either direction are equally likely, and results from such tests should be regarded as a starting point of further investigation, especially if deleterious results are achieved. In some cases, however, it may be quite possible to authenticate the validity of a threshold model by experimental evidence, and this certainly should be accepted in any reasonable system of assessment of probable drug hazards. On the other hand, much ingenuity is required to suggest a range of animals, of their genetic variation, and of environmental contexts for the testing of drugs that can begin to simulate the conditions of exposure of the human population. For these reasons it is probably untrue that animal testing can predict all possible human hazards. It therefore must be supplemented by more careful epidemiological scrutiny than is possible at the present time. In many cases metabolic analysis should be as reliable a predictor of potential trouble spots as the purely empirical testing for toxicity which is now mandated.

be able to anticipate them before there has been appreciable human exposure.

More insidious problems arise from compounds which have a low order of toxicity or which may take many months or years before they exert toxic effects in man. The most striking and perhaps most frightening example is the dye stuff intermediate, beta-naphthylamine, which has been responsible for epidemics of bladder cancers among chemical factory workers. Epidemiological studies here showed that a large proportion of workers who were chronically exposed were at risk of bladder cancer that appeared only after an interval of 10 to 15 years following initial exposure. The more recent discovery that the therapeutic synthetic hormone, DES, taken by mothers during pregnancy could induce the appearance of vaginal cancer in their daughters 15 or 20 years later is an object lesson of comparable dimensions. And the thalidomide tragedy, of course, has been the turning point for political attention to the problem of drug safety.

The unhappy truth is that none of the regulatory procedures that have been developed with the intention of responding to these threats is likely to be a particularly effective means of preventing similar mishaps in the future! None of these forms of toxicity had a well-established base of scientific knowledge or of biological detection prior to their occurrence as a human disaster. After the fact it has been possible to develop test systems that might have indicated some reason for caution for any of these agents, but their specificity and efficacy are subject to very serious doubt. The principal measure that would have some hope of minimizing the health impact of hazardous introductions, or for that matter of natural or synthetic compounds already in long use, would be a systematic collection of health data which has been strenuously resisted by civil libertarians on the grounds of possible abuses of privacy. Half-way measures, such as voluntary reporting of adverse drug effects, have been initiated, and if they are vigorously pursued may be some help in addressing the problem. But the principal emphasis in enforcing

safety testing has been on work with animals along lines that tend to encourage the large-scale collection of routine data rather than the establishment of creative investigations that look for problems on the basis of some theoretical rationale. Such procedures are likely to err in both directions because of the very serious difficulties of extrapolating from animal to the human context. Many dangerous compounds will be overlooked, or their hazards underestimated; on the other hand, many substances whose benefit-risk ratio is in fact highly advantageous for human use may be unfairly excluded.

One possible remedy would be to introduce another stage in the introduction of a drug intended for widespread use, namely its initial availability to a somewhat limited group of practitioners who have the necessary qualifications of education and experience to assist in the assessment of a new drug applied in practice to large numbers of patients, and who have a moral and legal obligation to cooperate in such an evaluation. Although such a procedure has no specific legislative authorization, something closely akin to it was adopted for the introduction of L-dopa for the treatment of Parkinson's disease with results that have been the source of widespread congratulation as an innovative procedural step, as well as a more sober appreciation of the benefits and the side-effects of the drug. Meanwhile, for many drugs we must make do the best we can with animal experiments, attempting to gain the outmost possible by way of prediction of human hazard.

A thorough analysis of the predictive value of animal data, and the limitations that arise from many sources, has yet to be made. It is perfectly obvious that the literal language of the Delaney amendment, which would forbid the use of a food additive (but not a drug!) upon any evidence that it could cause cancer in any animal when fed to any degree, has no scientific justification. It is certain that there are many natural food constituents that would eventually have to be disqualified also under a literal reading of the language of that law. In recent

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he years, it has become perfectly evident, however, that scientific judgment in the interpretation of the significance of animal findings does play a role in the regulatory procedure; the potential threat of arbitrary exclusions of compounds under the Delaney principle will be better remedied by improvements in the scientific cogency of such judgments than by changes in legal phraseology. And Mr. Hutt, speaking from this same platform, has pointed out that most if not all of the regulatory actions that concerned the cancer potential of food additives have been justified by the general responsibility of FDA for food safety and did not depend on the Delaney amendment per se. Since it has been known for many years that food as such can induce cancer--that is to say that underfed animals tend to have lower rates of cancer in general--it is obvious that a great deal of scientific judgment must enter into the evaluation of the risks to human health that may be pointed to by animal experiments with specific additives.

While routine testing, often demanded in a number of species, may result in very costly expenditures for the validation of an additive or a drug, current regulations do not require thoughtful analysis of the metabolism of a new agent. Indeed, the diversion of funds for rote private testing is a positive deterrent to the rational investigation of a proposed new compound. With metabolic information it will often be possible for insightful investigators to formulate hypotheses of possible sources of trouble that could lead to critical tests likely to be far more cost-effective than the current procedures. For example, cyclamates may well go through several cycles of review on account of their economic importance--less to the producers than to food processors--and also in response, perhaps, to the wants of a segment of the consumer public. To undertake costly experimentation on still more batches of rates with cyclamate itself is not very close to the point in view of recent knowledge that the likely source of the chronic toxicity of of this sweetener is almost certainly the metabolic product cyclohexylamine. What-

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ever the disposition of this compound in rodents, it is clear that a proportion of human beings eventually metabolize cyclamate to yield cyclohexylamine, perhaps with the help of modified intestinal flora that develop during chronic feeding with this agent. The testing of cyclohexylamine, and its further oxidation products, is likely to lead to a decisive understanding of the level of risk associated with cyclamate far sooner and at much less cost than continued agonies with the original raw material. In view of the demonstration of N-hydroxycyclohexylamine as a metabolite of cyclamate, and the chemical analogies of this compound with other biologically active and vicious derivatives of hydroxylamine, the outcome of such experiments is to some degree predictable but not yet their actual quantitative impact.

With this as with many other products we face the following dilemma in establishing empirical protocols. Most food additives and many drugs offer benefits that may be very large in the aggregate but would still not be worth the risk of substantial mortality arising from their use. Few people would defend the continued availability of a food additive that could be predicted, for example, to result in say 100 deaths per year. But for a consumer population of, say, 100 million, we must be able to rule out toxic side-effects to a level of 1 per million exposed even to meet that criterion! There is simply no way to measure toxicities at that level with animals. Tests within the more nearly feasible range of 100 to 1,000 animals might well give a result of zero mortality, that is to say less than 1 per 1,000, without revealing a level of population risk that would be absolutely intolerable. Such discussions have been muddled by the assertion of the concept of a "no effect dose" in the absence of experimental and statistical procedures to demonstrate that "no effect" actually falls below the level of our policy concern.

What we are ordinarily obliged to do is revealed in Figure 3. In order to bring the level of perceptible effect within the scope of the statistics of a laboratory

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experiment, we consciously overdose the test animals at levels of 10, 100, or even thousands of times higher than would be the exposure of the human population. On the simplest assumption there might be a proportional relationship between the observed toxicity and the concentration of the agent used, and we might then hope to establish rates of toxic side-effect that could then be used for policy purposes. This would be indicated in Figure 3 by the straightforward linear extrapolation.

This is not necessarily the way a particular agent works. Indeed, for certain types of toxic effect it is reasonable to suppose that lower doses can be accommodated by the metabolic machinery of the subject in such a way that the harm to each individual is negligible and the serious or lethal outcome most unlikely to occur. Agents that are direct cellular poisons, or that influence processes like transmission of the nerve impulse, may well fall in this category.

On the other hand, there are many compounds whose effect on the cell is believed to be quantal, all or none. This applies particularly to mutagenic agents and probably likewise to carcinogens. Here a single molecule, attaching to a vital target, may be the ultimate agency of harm. Then the dose effect relationship boils down to the statistical probability of a given molecule being able to reach a specific molecular target. Although the body could well tolerate the eradication of a substantial number of single cells, if one of them effectively becomes a cancer clone, this may be sufficient to eventually kill the host. For such agents a linear relationship between lethal probability and dose is entirely reasonable on theoretical grounds. This model also is admittedly oversimplified. The metabolism of the compound before it reaches its eventual target may well be different at lower and at higher doses, as well as between specific experimental animal species and man.

While these effects may tend to exaggerate the toxicity of an agent at low levels, there are other phenomena, such as metabolic variation among individuals and interactions with other chemicals and with disease states, that would operate

in a more grievous direction. The extrapolation from high doses to low ones by a linear function therefore would appear to be entirely justified as a first order procedure, but one that ought to be susceptible to criticism and rebuttal if additional experimental information is afforded. The production of tumors in mice with high doses of cyclamates is provocative rather than conclusive evidence that a lower but proportional rate of cancer would be produced at a lower level of this agent. But it is a warning that needs to be respected until and unless explicit contrary information can be exhibited that shows that the toxic side-effect is more than proportionally reduced at lower doses of the agent. And in this case, of course, we would have to pay close attention to existing knowledge of the metabolism of the agent.

Unhappily we have really no very satisfactory examples of empirical studies on the toxicity-dose relationship of food additives or drugs. The accumulation of evidence for carcinogens like the polycyclic hydrocarbons cautions us that the situation is, to say the least, quite complicated; and these studies also do not exclude a variety of intervening variables like cigarette smoking and individual variability. A widely observed effect with carcinogenic substances is not only a reduction in the frequency of the tumor lesions with lower doses, but a prolongation of the latent period before they become established. This finding tends to speak for a systemic as well as a cellular component in the toxicity of these agents, and similar remarks can be made for radiation. The model that is often evoked is that a carcinogen, besides initiating a tumor clone, must also interact with some induced or spontaneous depression of the mechanism of immune surveillance before the cancer can be expressed. We will face great difficulties, of course, in evaluating chemical substances for carcinogenesis as long as we remain so ignorant of the mechanisms by which they operate. However, these very complexities offer little reassurance about the security with which new agents can be used because they point to the possible interaction

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with a wide variety of other environmental circumstances which inevitably occur in the overall human population and which would be impossible to deal with in controlled experiments.

One example has been published of dose effect relationships with a chemical carcinogen namely beta-naphthylamine, the substance already mentioned as a cause of bladder cancer. In an attempt at quantitative dose effect study, Conzelman and Moulton were able to induce bladder tumors in 24 out of 34 dogs exposed to beta-naphthylamine for periods of 6 to 26 months. At the levels used many of the dogs had multiple tumors, a fact that taken together with the limited number of animals makes it difficult to draw quantitative conclusions about the dose effect relationship. They obtained numerous tumors, however, after more extensive latent periods, with the lowest dose levels--6mg/kg body weight daily--and believe they had indications that a given total dose was even more effective if administered over a longer period of time. Such a result is theoretically reasonable in circumstances where the initial compound must be metabolized to yield the final cancer producing product and where the metabolic system for doing this may become saturated. However, the data in this and other cases are still too scanty to justify the drawing of general conclusions at this time.⁽⁴⁾

(4) It should be noted that the FDA has adopted a quantitative definition of safety in its recent proposed regulations for analytical termination of residual hormones used in animal feeds. In effect, these regulations require standards that can be justified as resulting in a risk of not greater than one per 100 million consumers exposed in practice. The severity of this standard is somewhat mitigated by being based on the assumption that men and mice will respond to cancer at the same rate at a given concentration of carcinogen in their diets. While some mouse strains have been bred for high sensitivity to cancer, the rapid metabolism of the mouse, its shorter life span, and its smaller target volume may theoretically make it rather less sensitive a unit than is the human. We have no experimental data that would enable this point to be criticized empirically.

The Kefauver amendments of 1962 may be thought of as a social experiment that itself deserves critical evaluation; can the procedures of rigorous prior testing of drugs be verified to be both safe and efficacious, the criteria that the drugs themselves must meet? Dr. Sam Peltzman, professor of economics at UCLA, has attempted such an evaluation which has received some notice through Milton Friedman's column in Newsweek and through testimony before the Nelson Committee. The data he uses are essentially those appearing in Figure 4. They are historical and economic analyses of what has happened to drug introductions in the United States since the time of the Kefauver explosion of concern about safety and efficacy, and we will divide drugs into old, or pre-Kefauver, and new, or post-Kefauver. It is perfectly obvious that there has been a drastic reduction in the number of new chemical entities that have been introduced in the United States since that period. It is reasonable, although by no means proven, that the rigors of testing are an important reason both from the standpoint of rejection of candidates and the cost-deterrence to proceeding with certain lines of innovational effort. Commensurate with that reduction, there has been a very large escalation in the average investment per successful drug outcome. (These data only go up until 1968. I simply have not been able to find any more recent information.)

Now Peltzman does not firsthand make a statement as to whether this is good or bad. He is asking a question as to whether there are methods of assessing the social utility of this increase in development cost per drug on the market from something like \$5 million per new agent in 1960, to what must be approaching \$50 or more million. Are we getting anything for this? Peltzman says that he does not know anything about medicine, but that as an economist he will ask about market behavior; if a new regime of rigorous testing has resulted in more efficacious products, then these "new" drugs ought to be competing more favorably than old ones in a marketplace which is presumably dominated by expert consumers, namely physicians.

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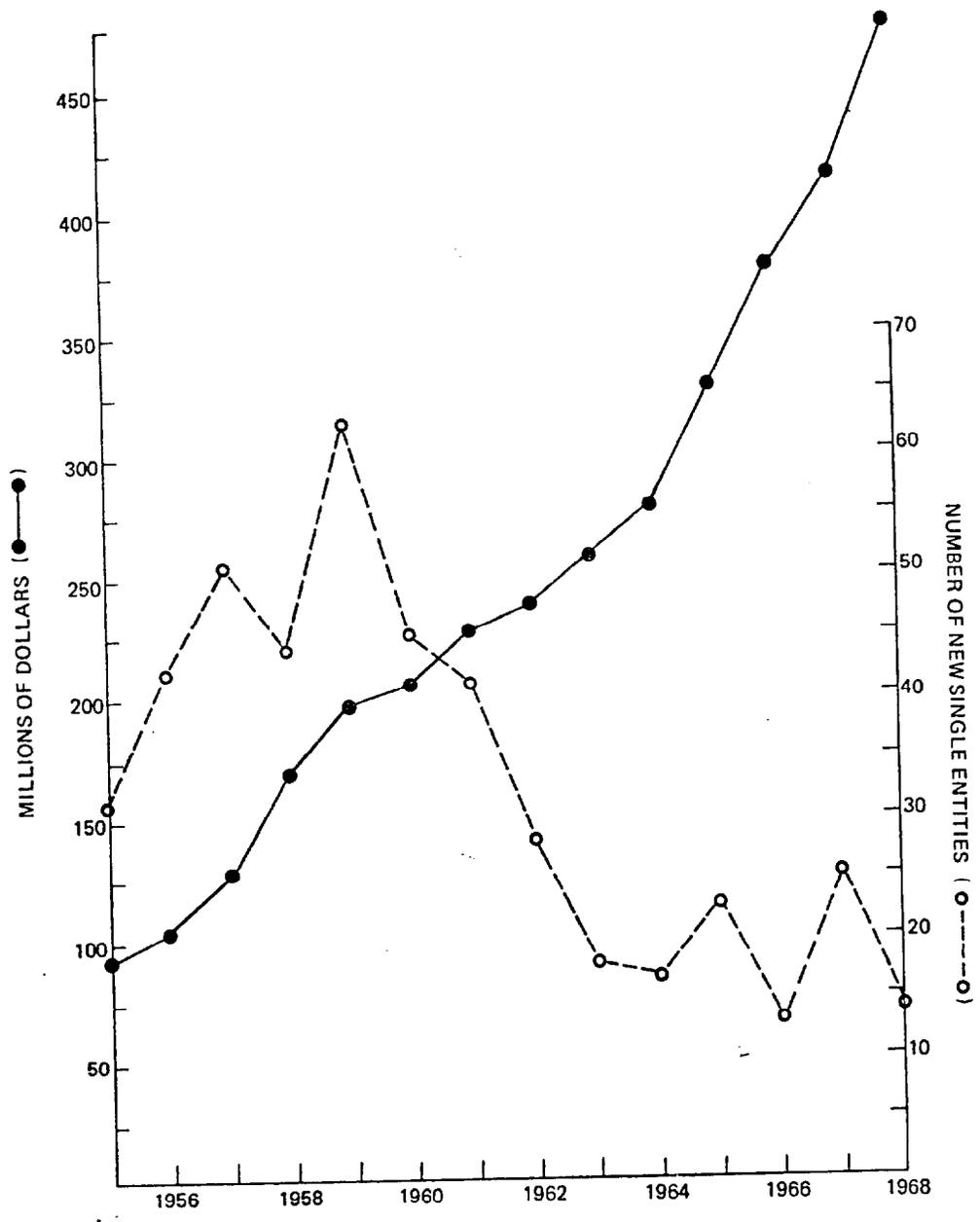


FIGURE 4: Research and development expenditures for prescription drugs versus basic new products introduced from 1955 to 1968. Source: National Institute of Neurological Diseases and Stroke, Section on Epilepsy.

His finding is that their behavior is about the same. This is to say with respect to the life cycle of the drug, to its market share, to the other economic measures he has been able to adduce, that the drugs which have successfully passed this tight filter of the post-Kefauver area have fared no better in the judgment of physicians than the ones that were there before.

His model might be summarized as saying that it appears as if there is a constant number of entities on the market at any one time, that they are simply turning over more slowly at the present time than before, and that the more recent introductions are showing no unique behavior in professional market response than the previous ones. I have not examined his assertions in any great detail, but even if they are granted, there are other possible interpretations. They are either very praiseworthy or very pejorative about the physicians who are making the basic consumer choices. You could say, for example, to explain these results that prescribing-behavior is random: that it has no relationship to the therapeutic efficacy of various agents, that the reason the new ones are doing no better than the old on the market is that in spite of having been screened more carefully for therapeutic efficiency, the doctors are choosing them at random or they are being selected for advertising on criteria that have no relationship to therapeutic use.

Alternatively, in the post-Kefauver era, many physicians are approaching a state of rational therapeutic nihilism: that is, one of very great skepticism about drugs in general, but especially skepticism about new introductions even if the FDA has certified them with respect to efficacy and safety. They are relying on the drugs that they have learned to love and learned to trust over long periods of use. This resistance to change now compensates for asserted advantages of the new agents so that they remain more or less at par.

Many other models are, of course, entirely possible to try to interpret what has been going on both with respect to innovation and to these choices. If the

rate of therapeutic innovation seems to be slowing down, many other aspects of national life are much less exuberant today than they were in 1960, and must be for very different kinds of reasons. This is not to dismiss the problems of loss of incentive about which many industry people have been agonizing. They believe that it is becoming increasingly difficult to rationalize the sinking of research funds into very long-term projects which may require even 15 or 20 years before a profitable return can be anticipated. Drug companies are obviously not going broke in large numbers; but that is a different question from whether they have the motivation to invest their resources in creative research. It is far safer to concentrate on marketing and on the kinds of research that may have a more immediately visible and early payoff--the so-called "me too" syndrome.

In any case, there is the possibility that by raising the price of admission to the drug production game, the Kefauver amendments must have worked to reduce competition and favor a monopolistic trend. There can be no retreat from the principle of demanding and somehow paying for critical research needed to ensure a high quality of new drugs. The urgent problem is to identify the waste in these procedures, especially to bring the drug development cycle back to a reasonable time.

In an ideal market system these matters would be of less concern. The retail price of new, effective drugs would indeed be encumbered by the implicit costs of testing for the ones that had to fail in order to bring the successful product to light. If it is true that the consumer benefit from drugs is already a large multiple of their retail price, there should be considerable room for that expansion. There are problems of unfair and therefore inefficient competition between grandfather products and new ones, but these would dissipate over the course of time. The public rather than the industry should be primarily concerned about the absorption of these rigorous testing costs and the delays that are inevitable in the introduction of new drugs, however efficacious, in a system that is designed to

assure that ineffective and unsafe ones have no chance of being permitted. I do not agree with Professor Peltzman that the largest credible magnitude of a safety defect in a drug is smaller than the benefits likely to accrue from the earlier introduction of some life-saving wonder-drug. The potential for mischief from, for example, another naphthylamine with a prolonged latent period is enormous. So there is potentially a great problem of safety--the question is whether the testing procedures as implemented during the last decade have made a crucial contribution to safety. Perhaps they have, more by disseminating a general sensitivity to the safety issue than by the relevance of the specific procedures. Both the costs and benefits of this atmosphere probably have more to do with deterrence, that is non-introduction of products, than with the visible market.

Lately the FDA has given evidence of responsiveness to the issue of the life-saving potential of a new introduction. And surely delays in optimal therapy owe at least as much to the inadequacy of new drug information among doctors, to maldistribution of medical care, and to obstacles of basic research and its interface with drug development than they do to FDA policies.

An important concern still is the evident degradation of morale in the research groups of many drug companies under the impact of the regulatory procedures themselves, and perhaps even more of the public and political criticism that has been directed at the industry. This problem of the social value placed on their services can be epitomized in the price that a truly wonderful new drug, having to bear large costs of development and of testing, might be expected to bring in the marketplace. In principle why should not such a prescription be imagined to command as high a price as brain surgery--assuming that the benefits of the drug and the general competitive situation were in other respects comparable? Many drugs have been marketed that had consumer benefits of this magnitude--most of the early antibiotics for example--but it is precisely the genius of American industry to have

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been able to multiply the supply of such agents in a way that is simply not possible for competent brain surgeons. Only in the case of rather rare diseases would the price of the drug have to approach that of other aspects of medical care to return a profit that would recapture the costs of development. There are such markets where the number of potential consumers is relatively small, say in the thousands, and where it may nevertheless be necessary to invest many millions of dollars for their development. We must then ask, what is the political feasibility of a life-saving pill that costs \$1,000?

I know that many drug companies simply cannot visualize finding themselves in a situation where they would, of course, be accused of being bloodsuckers if they demanded actual payment at these exorbitant levels. It would be safer not to get into such a political conflict to begin with! In some specific situations, groups of interested patients and their families might band together to help subsidize the costs of development either directly or by acting as political lobbies for government response. At such prices, government or other organized groups, such as insurance companies, are likely to bear much of the brunt of actual payment--they may still find it a good bargain--and some political clarity may still be achieved by more prior discussion of these principles. The dilemma is that everyone wants more safety and more efficacious drugs, but we have not quite agreed how this is to be paid for!

The problem of the \$1,000 pill is, of course, a political one as well as a technical and economic one, and it may be further battered by being confused with some other problems of equality of access to health. There has been some discussion about consumer representation and what technical expertise this could bring to bear in decisions about policy. I think some of this may have partially missed the point. Technicians and scientists like myself are very hung up on efficiency. We would like to see the maximum gain for our investment. We would like to see

an average increase in the overall health of the population. Taking a statistical and aggregated point of view, we have the broad vision to accept considerable variation in who will receive those benefits. Provided everybody benefits a little, we are willing to accept that some people may benefit a very great deal; at least rather than average gain than none at all. Not everyone thinks that way. It is certainly one of the axial conflicts of modern life that there are many who value equality of access to the care that is available and the equality of exposure to risk even higher than the absolute benefits. In effect, they would rather see everyone suffer the same ills and have equal access to the same gains, even at the expense of some share for everyone.

This is not something that can be or ought to be rationally decided, but we would be foolhardy not to recognize that this is an important aspect of our culture. It is one that politicians who have to be elected must understand very well. Some of the conflicts that we have heard about, I think, reflect inadequate understanding of the role of the two principles of equality and efficiency in contemporary life. It is the egalitarian point of view, more than any special technical expertise or even partisan consumer constituencies, that may have to be fairly represented in the development of further policy.

Finally, I would like to comment on the need to reconstruct our approach to safety testing. Generally we should be more concerned about regarding safety testing as a research problem and not as an obstacle course. You do not learn very much about the physiology of muscle contraction by setting up obstacles to see which drug can hurdle them and which cannot, and there is then very little generalization possible from one agent to the next in the way that testing is done today.

As we have escalated from a few millions to a few hundreds of millions of investment in this particular area, it seems to me a matter of great social urgency that these funds not be wasted in merely determining whether a particular agent is

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going to make it from a regulatory standpoint or not. The publication of the information that has been gleaned on a particular drug would, of course, be the first step. But this must go much further into the basic experimental design of determining what kinds of drugs are safe and what kinds of tests are going to elicit relevant information about them.

To do this will require a somewhat more broad-minded attitude and more discretionary power (yes, on the part of the FDA) in taking account of all available evidence, of demanding information about metabolism. Especially, they will have to give credit to information about related compounds which may have been very thoroughly worked over and where very rationally the substitution of an ethyl for a methyl group is extremely unlikely a priori to have very much impact on safety outcome. Not that you do not make some tests for it, but it is absurd to have to go through exactly the same routine in validating the safety of closely related derivatives of drugs that have been quite thoroughly tested as for totally new kinds of structures. I am not aware that this is part of regulatory policy at the present time.

In fact, there are any number of horror stories about drug companies that have contemplated the evolution of a product from an impure mixture to a pure compound, or reduced its dose, or discovered improved formulations involving the substitution of different salts, and have been deterred from bringing these innovations to the market. In spite of the fact that they have every inherent likelihood, even a certainty, of improving both the safety and the efficacy of the drug, the routine regulatory procedures believed to be required by the FDA are regarded as prohibitive. Perhaps these fears are fantasies or may be connected with some less obvious information that also bears on the utilities of these advances. If they are not fantasies then the FDA itself has a task of communication ahead of it. There is a story, however, that is not so apocryphal concerning

certain soft lenses which must be labeled "safety in pregnancy has not been substantiated," a level of bureaucratic thinking that surely would deter the advancement of creative innovations. This kind of regulation may even be a satire intended to draw attention to the absurdities in the system. It would be funnier if we did not face enormous problems in determining the actual teratogenic and mutagenic hazards that probably do attach to a variety of products that have been on the market for some period of time.

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